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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/802,466	03/09/2001	Paul D. Taylor	P-408	7041

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EXAMINER	
MARVICH, MARIA	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 03/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/802,466	TAYLOR ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,6-11,21 and 26-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6-11,21 and 26-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to a request for continued examination filed 1/20/05 and an amendment filed 3/2/05. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/2/05 has been entered. Claims 3, 5, 12-20, 22-25 and 29-33 have been cancelled. Claims 1, 7 and 28 have been amended. Claims 1-2, 4, 6-11, 21 and 26-28 are pending in the application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4, 6-11, 21 and 26-28 are rejected under 35 U.S.C. 103(a) as being anticipated by Gjerde et al (US 2003/0165941; see entire document) in view of Bloch (5,866,429; see entire reference) **This is a new rejection necessitated by applicants' amendment.**

Applicants claim a method for stabilizing an RNA molecule against degradation in which a solution of RNA and an agent capable of degrading the RNA and a counter ion are applied to a non-polar separation surface. The column has an internal diameter of greater than 5.0 mm. The

RNA is eluted from the separation medium by a mobile phase comprising an organic solvent in which the mobile phase is controlled by a mobile phase flow control using MIPC.

Gjerde et al teach separation of polynucleotides by Matched Ion Polynucleotide Chromatography (MIPC) also referred to as HPLC-based ion pairing Chromatography and furthermore by denaturing MIPC (dMIPC) (page 3, paragraph 0023 and paragraph 0030 and page 4, paragraph 0037). Multivalent cations are removed from all aspects (page 11, paragraph 171). DMIPC involves separation in temperatures ranging from 50°C to about 75°C. Samples are applied to separation media such as silica that support non-polar organic polymers or long chain C1 to C24 hydrocarbon groups bound to inorganic substrate (page 30, paragraph 417-418) and has an average diameter of 1-100 microns (page 28, paragraph 395). The method comprises contacting the separation media with eluting solution A consisting of 0.1 M TEAA pH 7.2 and solution B that consists of 0.1 M TEAA and 25% acetonitrile (page 35, paragraph 0467). The method is performed using computerized controls and a mobile phase flow control means designed to control the flow of solvent and aqueous phases (see e.g. page 7, paragraph 0082-0084). Given that the process involves addition of mobile phase in gradients and multiple steps, the method is best adapted to a batch process (see page 18, paragraph 253). The procedure disclosed by Gjerde et al is the same as that recited in the instant claims and taught in the instant Specification. Therefore, and absent evidence to the contrary, it would reasonably be expected to yield RNA that is substantially free of agents capable of catalyzing degradation of RNA. Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the

products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Gjerde et al do not teach that the column has an internal diameter of greater than 5.0 mm.

Petrovic and Jankovic and Bloch teach that the internal diameter of the columns can be greater than 5 mm. Petrovic and Jankovic teach that the column in simple ion exchange methods for RNA separation can be between 4-6 mm naturally encompassing those diameters that are greater than 5 mm. Bloch et al teaches that the column can be no greater than 10 mm also encompassing diameters that are naturally greater than 5 mm. Bloch teaches that the column is the most important component of HPLC which is used in the MIPC method. The diameter in both Bloch and Petrovic and Jankovic can be greater than 5 mm.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include the internal diameter sizes taught by Bloch and Petrovic and Jankovic with the method of separation of RNA molecules taught by Gjerde et al because Gjerde et al teaches that it is within the ordinary skill of the art to separate RNA using non-polar separation medium in which a mobile phase is passed through to elute RNA and because Bloch and Petrovic and Jankovic teach that it is within the ordinary skill of the art to use columns with internal diameters of greater than 5 mm. One would have been motivated to do so in order to receive the expected benefit of preferred components for RNA separation. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 7-10, 26 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oefner (US 6,453,244 B1; see entire reference) in view of Bloch (5,866,429; see entire reference) **This is a new rejection necessitated by applicants' amendment.**

Applicants claim a method for stabilizing an RNA molecule against degradation in which a solution of RNA and an agent capable of degrading the RNA and a counter ion are applied to a non-polar separation surface. The column has an internal diameter of greater than 5.0 mm. The RNA is eluted from the separation medium by a mobile phase comprising an organic solvent in which the mobile phase is controlled by a mobile phase flow control using MIPC.

Given that MIPC also referred to as HPLC-based ion pairing Chromatography is defined in the instant specification as a process for segregating RNA using non-polar reverse phase media wherein the process uses a counterion and an organic solvent (see page 11, line 11-14), the method of Oefner et al can be considered to be MIPC. Oefner teaches elution of RNA with a mobile phase containing an ion-pairing reagent and organic solvent under denaturing conditions such as heat or chemicals (see e.g. abstract). Specifically, Oefner teaches isolation using ion pairing reverse phase HPLC in the presence of a counterion and organic solvent (see column 11, line 65 through column 12, line 12). The solid support is comprised of silica and the mobile phase is comprised of TEAA and acetonitrile (see e.g. column 4, lines 7-29). Denaturing conditions include temperatures up to 70°C to 80°C (see e.g. column 4, line 46-53). The separation media has an average diameter of 1-100 microns (column 11, line 24-25), the concentration of TEAA is about 0.05 to 1.0 Molar and about 25% acetonitrile (see e.g. column 12, line 31-55). The present invention can be used in the separation of RNA (see e.g. column 13, line 1-20) and the procedure can be used for large numbers of samples to be analyzed (see e.g.

column 14, line 40-48). Columns comprised of PEEK are used (see e.g. column 8, line 28-45). The procedure disclosed by Oefner et al is the same as that recited in the instant claims and taught in the instant Specification. Therefore, and absent evidence to the contrary, it would reasonably be expected to yield RNA that is substantially free of agents capable of catalyzing degradation of RNA. Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Oefner et al do not teach that the column has an internal diameter of greater than 5.0 mm.

Petrovic and Jankovic and Bloch teach that the internal diameter of the columns can be greater than 5 mm. Petrovic and Jankovic teach that the column in simple ion exchange methods for RNA separation can be between 4-6 mm naturally encompassing those diameters that are greater than 5 mm. Bloch et al teaches that the column can be no greater than 10 mm also encompassing diameters that are naturally greater than 5 mm. Bloch teaches that the column is the most important component of HPLC which is used in the MIPC method. The diameter in both Bloch and Petrovic and Jankovic can be greater than 5 mm.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include the internal diameter sizes taught by Bloch and Petrovic and Jankovic with the method of separation of RNA molecules taught by Oefner because Oefner teaches that it is within the ordinary skill of the art to separate RNA using non-polar separation medium in which

a mobile phase is passed through to elute RNA and because Bloch and Petrovic and Jankovic teach that it is within the ordinary skill of the art to use columns with internal diameters of greater than 5 mm. One would have been motivated to do so in order to receive the expected benefit of preferred components for RNA separation. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1, 2, 4, 6 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oefner (US 6,453,244 B1; see entire reference) in view of Bloch (5,866,429; see entire reference) further in view of Petro et al (6,260,407; see entire reference). **This rejection is maintained for reasons of record in the office action mailed 2/13/04 and 7/26/04 and 1/14/05 and is restated below.**

Applicants claim a method for stabilizing an RNA molecule against degradation in which a solution of RNA and an agent capable of degrading the RNA and a counter ion are applied to a non-polar separation surface. The RNA is eluted from the separation medium by a mobile phase comprising an organic solvent in which the mobile phase is controlled by a mobile phase flow control using MIPC.

The teachings of Oefner are described above and are applied as before except; Oefner does not teach a mobile phase control means that is controlled by a computer.

Petro et al teaches that the mobile phase of a liquid chromatography system is controlled by a flow control means, which in turn is controlled by a computer. Specifically, the mobile

phase solutions are stored in reservoirs and have dedicated pumps that are controlled by computer (see e.g. figure 6 and bridging paragraph column 37-38).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include the computer controls taught by Petro et al with the method of separation of RNA molecules taught by Oefner because Oefner teaches that it is within the ordinary skill of the art to separate RNA using non-polar separation medium in which a mobile phase is passed through to elute RNA and because Petro et al teach that it is within the ordinary skill of the art to control the mobile phase using control means and computers. One would have been motivated to do so in order to receive the expected benefit of generating a high-throughput automated sampling system (see Petro et al, e.g. abstract). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 11 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oefner (US 6,453,244 B1; see entire reference) in view of Bloch (5,866,429; see entire reference) further in view of Petro et al (6,260,407; see entire reference) further in view of Sheridan and Sheridan (Scientist 3(4):23 Feb 20, 1989; see entire document. **This rejection is maintained for reasons of record in the office action mailed 2/13/04 and 7/26/04 and 1/14/05 and is restated below.**

Applicants claim a method for stabilizing an RNA molecule against degradation in which a solution of RNA and an agent capable of degrading the RNA and a counter ion are applied to a non-polar separation surface. The RNA is eluted from the separation medium by a mobile phase

comprising an organic solvent in which the mobile phase is controlled by a mobile phase flow control using MIPC under conditions free of multivalent cations.

The teachings of Oefner and Petro et al are described above and are applied as before except; neither Oefner nor Petro teach that conditions of separation are free of multivalent cations.

Sheridan and Sheridan et al teach a Metal-Free column system for use in chromatography in which the recovery of biopolymers is improved (see e.g. page 2, paragraph 5). Sheridan and Sheridan use for example PEEK (polyether ester ketone), which is a non-metal polymer (page 2, paragraph 5). Metals are considered the source of multivalent cations.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the conditions taught by Oefner with the metal-free conditions taught by Sheridan and Sheridan because Oefner teach that it is within the ordinary skill of the art to use PPEK columns for separation of RNA and because Sheridan and Sheridan teach that it is within the ordinary skill of the art to use metal-free conditions in chromatography. One would have been motivated to do so in order to receive the expected benefit of improved recovery that occurs with metal-free conditions. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments

Applicants traverse the claim rejection under 35 USC 102 and 103 on pages 8-9 of the amendment filed 3/2/05. Applicants' argue that Gjerde et al and Oefner do not teach that the

RNA is separated from an RNA degrading agent thereby stabilizing the RNA against degradation. As well, applicants argue that the references do not teach conditions for achieving such separation. For example, separation columns with an inner diameter of greater than 5 mm dramatically improve RNA fractionation. Applicants argue that neither Petro et al or Sheridan and Sheridan cure the deficiencies of the primary references.

Applicant's arguments filed 3/2/05 have been fully considered but they are not persuasive. Oefner and Gjerde et al teach RNA separation by the exact same methods as those recited. Absent evidence to the contrary, the methods would be expected to separate RNA from RNA degrading agents. Use of columns for RNA separation that are greater than 5mm have been used in the art (see Bloch and Petrovic and Janovic). That these conditions result in increased RNA yield has not express basis in the claims and therefore does not impact the claims. Rather it can be argued that use of columns with diameters of greater than 5 mm was known in the art and given that it is a preferred embodiment in Bloch et al, it would have been obvious to a person of skill in the art to use columns with internal diameters that are greater than 5 mm.

Conclusion

Claims 1, 2, 4, 6-11, 21 and 26-28 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 11, 2005

GERRY LEFFERS
PRIMARY EXAMINER